approximately to postrhinal cortex in rats and areas TF and TH in non-human primates [14]. It receives strong projections from visual cortex (and cortical association areas) and in turn provides a dominant input into entorhinal cortex but projects also directly to the subiculum and the hippocampal subfield CA1 [14].

The parahippocampal cortex thus lies at the interface between the spatial representational system in the hippocampal formation and the visual system (Figure 1), which makes it an ideal candidate to integrate external visual and internal spatial signals. Notably, the interaction between incoming sensory information and stored spatial representations has a cellular correlate. Single cells in the rat brain signal an animal's allocentric position in the local environment, suggestive of an internal cognitive map [15]. Two recently discovered cell types might be of particular relevance here: boundary-vector cells in the subiculum [16] and border cells in entorhinal cortex (and to a small extent also in the vicinity of postrhinal cortex) [17]. Interestingly, they were found in the two regions which receive direct input from postrhinal cortex. These cells encode the animal's position relative to geometric features in the environment, like walls and corners. The functionality of these cells could relate to observations in the two fMRI studies that the space-defining object effect in the parahippocampal cortex is driven by lower portability and greater size, [3] and also the finding that parahippocampal cortex activity reflects expanse (whether it is open or closed) of scenes [4] (see also [2,18]).

An interesting avenue for future research will be the investigation of how mechanisms of scene perception previously measured between the parahippocampal cortex and high-order visual areas in human and non-human primates — particularly the 'what' *versus* 'where' pathways [11] — correspond to findings in targeted electrode studies of rodents, human neuropsychology and neuroimaging studies implicating the hippocampal formation during active spatial exploration and spatial introspection [8,9,13,15,19,20].

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Evolution of Development: Diversified Dorsoventral Patterning

Patterning of the dorsoventral axis by graded BMP signaling is conserved in the evolution of animals. However, this system has also proven to be highly adaptable, as is now highlighted by its short-range function in the leech *Helobdella*.

Ethan Bier

BMPs and their antagonists establish the embryonic dorsoventral axis in many bilaterian groups, including chordates, cephalochordates [1], echinoderms [2], ecdysozoans, such as arthropods [3–5], and lophotrochozoans, such as annelids [6–8] (Figure 1). Indeed, the localized deployment of BMP patterning components predates the emergence of bilaterians, as embryos of several species of the radially symmetric cnidarians display asymmetric expression of these genes [9]. Although this is a matter of ongoing debate, graded BMP signaling appears to have been co-opted during axis formation in a basal bilaterian to determine the relative locations of a neuroectodermal domain giving rise

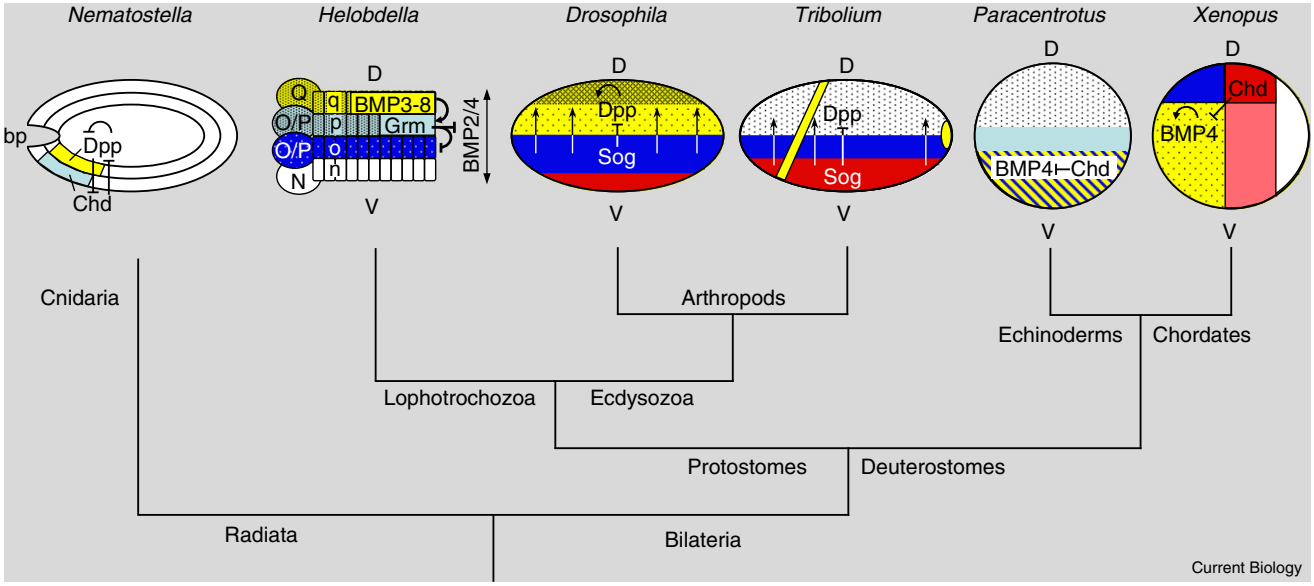

Figure 1. Evolution of dorsoventral patterning by BMP signaling.

Key features of BMP signaling in embryos of diverse organisms: the sea anemone *Nematostella*, the leech *Helobdella*, studied by Kuo and Weisblat [10], the insects *Tribolium* and *Drosophila*, the sea urchin *Paracentrotus* and the frog *Xenopus*. Phylogenetic relationships are indicated by the tree, which is not drawn to scale. Note that the dorsoventral (D-V) axis appears to have undergone an inversion in the chordate lineage, which includes vertebrates [1,11]. Red/pink indicates mesoderm; dark blue indicates CNS neuroectoderm; yellow indicates the domain of BMP expression, which corresponds to epidermal ectoderm in vertebrates, *Drosophila*, and *Helobdella*; the stippled region indicates region of known BMP activity, darker stippling indicates higher levels of activity; vertical arrows indicate vectorial Sog/Chd-mediated transport of BMPs. D = Dorsal; V = Ventral; Chd = Chordin; Grm = Gremlin; bp = blastopore. For more complete descriptions of the interactions between BMP pathway components in ectoderm patterning, see [11,13,14].

to a condensed central nervous system (CNS) and an ectodermal domain giving rise to the epidermis and peripheral nervous system (PNS). The epidermal and PNS domain is specified by high levels of BMP signaling, whereas inhibition of BMP signaling by antagonists such as Sog/Chordin, Noggin and Gremlin, defines the location of the CNS. Typically, the protein networks involved in long-range graded BMP signaling are not conserved in species in which cell lineage plays a dominant role in assigning cell fates. However, a new paper by Kuo and Weisblat [10] in this issue of *Current Biology* provides an intriguing example of ancestral BMP signaling components being adapted for short-range inductive interactions.

Generating Dorsoventral BMP Activity Gradients

Despite the highly conserved nature of BMP signaling components and their spatial expression along the dorsoventral axis in bilaterian animals, different networks of interactions between these components have been found in different species, revealing that this pathway is at the same time highly conserved and evolutionarily malleable. In the well-studied vertebrate and fruit fly embryos, BMPs and their antagonists are expressed in complementary patterns. Complexes form between BMPs and their inhibitors as well as other extracellular components such as metalloproteases in the BMP1/Tolloid family, which cleave the BMP antagonist Sog/Chordin, thereby releasing BMPs to signal. Diffusion of such BMP–inhibitor complexes creates broad gradients of BMP activity that can span the entire dorsoventral axis, subdividing the ectoderm into high versus low activity regions, as well as defining distinct cell fates within each of these domains (e.g., at specific thresholds of BMP signaling) [11–14].

However, in other species, such as echinoderms or corals and sea anemones [9], BMPs and their antagonists are co-expressed on the same side of the embryo; or, only one component is dorsoventrally localized, as in the case of ventrally localized Sog/Chordin in the flour beetle *Tribolium castaneum* [4] (Figure 1). Such an overlapping spatial arrangement of BMPs and antagonists can also create BMP activity gradients, as BMPs alone or in complex with antagonists can diffuse to establish domains of relatively higher and lower BMP signaling. Indeed, opposing and overlapping configurations of BMPs and antagonists are coupled in vertebrate embryos to create a robust self-regulating morphogenetic field of cells [15].

The BMP Network as a Short Range Inductive System

The new study by Kuo and Weisblat [10] now reveals just how flexible the BMP patterning system can be. The authors show that BMP patterning is employed in a novel way in an annelid, the leech *Helobdella* sp. (Austin), to specify ectodermal cell fates along the dorsoventral axis. In contrast to the embryos mentioned above, in which cell fates are not hard-wired by lineage, ectodermal cells in *Helobdella* derive from one of four possible lineages produced by four stem cells. These stem cells, called teloblasts (labeled Q, O/P, O/P, and N), produce four strings (named q, p, o, n from dorsal to ventral) of adjacent cell progeny (bandlets) organized in a parallel array that give

rise to epidermis (q), epidermis and PNS (p), CNS (o), and ventral midline (n) (Figure 1).

Given such defined lineage relationships in *Helobdella*, one might wonder whether graded BMP signaling would offer any advantage to dorsoventral patterning, as all that would be needed in principle is to confer distinct identities upon the stem cell precursors that generate the different bandlets. Indeed, in other species with lineage-based embryogenesis, such as the nematode *Caenorhabditis elegans* [16], or ascidians [17], many components of the BMP signaling network have been lost, and this signaling network seems to play little if any role in assigning cell fates along the early dorsoventral axis.

Kuo and Weisblat [10] identified a subset of known BMP signaling components that were candidates for contributing to dorsoventral patterning in *Helobdella*. RNA interference (RNAi) knock-downs and misexpression experiments revealed reciprocal effects of increasing versus decreasing BMP signaling on the fate of O/P lineages in embryos of *Helobdella* (*Hau*) and established the following key facts: First, *Hau-bmp2/4a,b* and their likely receptor *Hau-alk3/6* are expressed broadly throughout the germinal bands, while *Haubmp5-8* is expressed only in the dorsal-most q bandlet and *Hau-gremlin* is expressed only in the p bandlet (adjacent and ventral to the q bandlet). Second, when ectopically expressed, Hau-BMP5-8 can activate expression of *Hau-gremlin* and other p bandlet markers in both O/P-derived lineages, but in wild-type embryos this ligand acts only in a contact-dependent fashion on cells of the dorso-lateral p bandlet adjacent to the q bandlet. Finally, Hau-Gremlin can block signaling by Hau-BMP2/4a,b, but not by Hau-BMP5-8. The result of this arrangement of BMP pathway components is that Hau-BMP5-8 secreted by the q bandlet induces high level signaling only in the adjacent most dorsal of the two O/P lineages (p), which consequently results in those cells expressing the antagonist Hau-Gremlin. This localized expression of *Hau-gremlin* in p bandlet cells in turn blocks the response to the ubiquitously distributed Hau-BMP2/4a,b in the ventral most O/P lineage (o).

This sequence of inductive signaling across a single cell diameter leads to high levels of BMP signaling in the dorsal q and dorso-lateral p bandlets, where Hau-BMP5-8 signaling is active, and lower BMP levels in the ventral-lateral o bandlet, in which background Hau-BMP2/4a,b signaling is reduced by Hau-Gremlin, and no response to BMP signaling in the ventralmost n bandlet due to some unknown feature of its lineage determination.

Graded versus Inductive Patterning

The novel use of BMP signaling in *Helobdella* in a series of contact-dependent inductive events represents a clear departure from its typical role in long-range signaling as a morphogen. However, it is not without precedent that a signaling pathway can be used for both local and longer range signaling. For example, in the case of EGF receptor signaling, cleavage and diffusion of membrane tethered forms of TGF-α or Spitz in *Drosophila* can lead to long-range signaling over several cell diameters while several mechanisms have been defined that can restrict signaling to neighboring cells [18]. Similarly, signaling by the membrane-tethered ligand Delta to the Notch receptor can be deployed within a field of competent cells or be restricted to signaling between adjacent domains of cells in a for-export-only form of signaling [19] in which one group of cells produces a signal to which they cannot respond. This results in a response only in adjacent cells that are close enough to receive the signal. An extreme illustration of this type of signaling is the activation by Delta of the *single-minded* gene in a single row of mesectodermal cells abutting the *Drosophila* mesoderm [20].

An interesting question for future investigation is how the BMP regulatory network, which evolved originally to pattern tissues in a graded, threshold-dependent fashion, was then modified to act in a strictly local, for-export-only form of signaling. It will also be interesting to explore further the role of BMP signaling in very early *Helobdella* embryos when the primary axes are established. An important lesson from these studies in *Helobdella* and the explosion of new findings in other alternative model systems is that analysis of embryos with distinct developmental strategies deepens our understanding of both the BMP signaling network itself and how evolution can tinker with this ancient system to generate very different embryonic patterns.

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Centrosome Size: Scaling Without Measuring

Centrosome size is controlled by a limiting component mechanism in which a fixed quantity of precursor protein is divided up among however many centrosomes are present. This simple scheme explains size control and scaling of centrosomes relative to cell volume.

Wallace F. Marshall

The mechanisms that determine organelle size remain almost entirely unknown, but a new study, published in this issue of *Current Biology*, on centrosome size regulation during *Caenorhabditis elegans* embryogenesis has now provided evidence for an extremely simple mechanism that may apply to a wide range of other organelles [1]. Several theoretical mechanisms for organelle size control have been described — for example, molecular rulers, which represent protein molecules whose physical size determines the size of an assembling structure. Rulers have been shown to control length in bacterial injection needles [2] and bacteriophage tails [3]. Ruler mechanisms require a way to align the ruler relative to the assembling structure, and to read out the location of the assembling structure relative to the end of the ruler. Other schemes, such as feedback loops that measure and adjust organelle size, are even more complex.

Wouldn't it be simpler if there was a way to use the components of the structure itself as a way to control its size? Perhaps the simplest way to control the size of a structure is a limiting component mechanism, in which a cell produces a fixed quantity of precursor, which is then assembled into the final structure, such that the structure assembles until the precursor component is entirely exhausted from the cytoplasm. The quantity of precursor component produced by the cell would thus directly determine the size of the structure. If precursor concentration was the same in all cells at the time that assembly starts, then larger cells would form proportionally larger structures since they would contain more of the limiting component (Figure 1). This type of model can thus account for both size control and scaling of organelle size with cell size. The limiting component model is conceptually appealing, but how do we know if it applies in any given situation?

One way to test for a limiting component mechanism is to ask how the size of the structure varies as a function of the number of copies of the structure within one cell. If a cell makes M molecules of the size-limiting precursor, which must then be distributed among N copies of the organelle, then the average number of precursor molecules per copy is M/N, hence the size of the structure should be proportional to 1/N. Such a dependence means that, if a cell has two copies of the structure, the structures would be half as big as they would be if the cell had just one. In a cell with three copies, they would each be one-third as large. Alternatively, if you add up the volume of all the copies of the structure, the total volume should be constant, independent of the number of copies. Another hallmark of a limiting component system is that the growth rate of the structure should gradually slow down and reach a plateau as the limiting component is exhausted from the cytoplasm. Structures that cease growth abruptly when they reach a particular size would thus not be consistent with this type of model and one would therefore have to look for other types of mechanisms, such as rulers, to explain their size control.

This general idea of a limiting component model was first proposed by Kuchka and Jarvik [4] for flagellar length control in the green alga *Chlamydomonas reinhardtii*, a model system in which it was already known that reduced expression of precursor proteins resulted in decreased length [5]. Measurements in mutants that change the number of flagella per cell revealed that flagellar length decreased in cells with more flagella, but did not decrease as steeply with increasing number as the limiting component model would predict [6]. A simple limiting component model was thus ruled out in that system, and indeed there has not been a clear-cut example of a limiting component model for organelle size control until now.

In the new study, Decker and co-workers [1] examined the size of centrosomes in developing *C. elegans* embryos, in which all protein is provided maternally, hence the total quantity of centrosome precursor protein is fixed during the early divisions. What they found was that, as early divisions proceeded, producing more and more centrosomes in the embryo, centrosomes were smaller and smaller but the total summed volume of the centrosomes was indeed constant, as predicted by the limiting component model.

When individual centrosomes were examined and compared to the size of the cells that contained them, it was found that centrosome volume was linearly proportional to cell volume. This also fits with a limiting component model since the volume of the whole embryo is constant, and precursor is presumably distributed during cell division proportionally to the volume of the daughter cells, hence larger cells obtain a proportionally larger fraction of the initial quantity of precursor.

Decker *et al.* [1] further confirmed that centrosome size was truly cell-size